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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,072	01/02/2004	Sven Eyckerman	2676-624US	2266

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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
11/10/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTOMail@traskbritt.com

Office Action Summary	Application No.	Applicant(s)	
	10/751,072	EYCKERMAN ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,11,13,16 and 27-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,11,13,16 and 27-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 7/24/08 has been entered in full. Claim 1 is amended. New claims 27-30 are added.

Claims 1, 3, 11, 13, 16 and 27-30 are pending and are under consideration.

Election/Restrictions

In the original restriction requirement set forth on 10/7/04, Invention I was set forth as "a fusion protein comprising a ligand binding domain and a bait domain" (recombinant receptor) and Invention II was set forth as "a prey polypeptide" (see pg 2). New claims 27-30 are directed to a receptor complex comprising both a recombinant receptor encompassed by Invention I and a prey polypeptide encompassed by Invention II, a set of vectors encoding said complex, and a eukaryotic cell comprising said complex). Thus, new claims 27-30 are Linking Claims because they encompass both Invention I and Invention II.

Claims 27-30 link Inventions I and II. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claims 27-30. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Currently, there are no pending claims directed solely to Invention II.

Withdrawn Objections and/or Rejections

The objection to claim 1 at pg 2-3 of the 4/22/08 Office Action is *withdrawn* in view of Applicants' amendment to the claim.

Maintained Objections and/or Rejections

Claim Rejections – 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 11, 13, 16 and 27-30 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Eyckerman et al, 1999 (Eur Cytokine Netw. 10(4): 549-546; cited previously). This rejection was set forth at pg 3-6 of the 4/22/08 Office Action.

For clarity, the rejection is first reiterated, and then Applicants' arguments are addressed.

Eyckerman teaches recombinant receptors comprising the mouse leptin receptor with one or more tyrosine residue mutations in the cytoplasmic domain and a heterologous myc-tag polypeptide (pg 550, column 1; eight different receptors are disclosed each with different mutations). Eyckerman teaches that Tyr1138 is an activation site required for signaling in response to leptin binding ("Tyr to Phe mutations in the cytoplasmic tail of the mouse leptin receptor confirmed the critical role of Tyr1138 (a YxxQ motif) and STAT-3 activation for induction of leptin-induced genes in PC12"; see Abstract, pg 549). One of the mutant receptors taught by Eyckerman comprises two tyrosine mutations (Tyr985Phe and Tyr1077Phe) but retains the Tyr1138 activation site

(pg 550). This is the same combination of mutations (Tyr985Phe and Tyr1077Phe) and wild type tyrosine (Tyr1138) as used in the LepRFFY receptor described in Example 1 of the instant application (see Figure 1). This receptor meets all of the structural requirements of claim 1: "an extracellular ligand binding domain of a mammalian receptor" (e.g., mouse leptin receptor domain); a cytoplasmic domain comprising a domain derived from a cytoplasmic domain of a mammalian receptor (e.g., leptin receptor domain), at least one activation site that is a tyrosine residue (e.g., Tyr1138) and a heterologous bait polypeptide (e.g., the myc-tag), and wherein the cytoplasmic domain comprises at least a JAK binding site (Eyckerman teaches on page 549 that the leptin receptor includes a "a JAK tyrosine kinase binding site (Box 1)").

In addition to the above mentioned structural limitations, claim 1 contains the following functional limitation: "wherein the activation of said recombinant receptor is inhibited by binding of a fusion protein to said heterologous bait polypeptide, said fusion protein comprising a prey polypeptide and at least one of an inhibitor of the activation of said recombinant receptor that is selected from the group consisting of a member of the SOCS family, a JAK-phospatse [sic], and a STAT-phosphatase". Eyckerman teaches a receptor that meets all of the structural limitations of claim 1, but Eyckerman is silent as to whether the receptor has the functional limitation as claimed.

The examiner is unable to determine whether the prior art disclosure of the receptor taught by Eyckerman possesses the characteristic of being inhibited if contacted with a fusion protein polypeptide that binds to the heterologous bait polypeptide (myc tag) and comprises a prey polypeptide and a inhibitor of activation. With these conditions, where the product seems to be identical except that the prior art is silent to the characteristic or property claimed, then the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Note the case law of *In re Best* 195 USPQ 430, 433 (CCPA 1977).

It is stressed that the claims are directed to a genus of recombinant receptors, wherein the scope of the genus is partly defined by a functional interaction with a genus of prey polypeptides. The claims are not directed to the prey polypeptide *per se*, either alone or in combination with receptor. As such, the rejection of claim 1 under 35 U.S.C.

102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Eyckerman et al, 1999 does not require that Eyckerman actually teach a fusion protein capable of inhibiting the receptor. If the receptor described by Eyckerman is inherently capable of being inhibited when contacted with a fusion protein comprising a prey polypeptide and an inhibitor of activation (a member of the SOCS family, a JAK phosphatase or a STAT phosphatase), then it meets the functional limitations of the claim. As far as the Examiner can determine, the mutant receptor described by Eyckerman would be inhibited if contacted with a fusion protein described in the instant application (i.e., one comprising both a prey polypeptide and an inhibitor of activation).

Claim 3 depends from claim 1 and recites an additional functional limitation that "said recombinant receptor is activated by addition of a compound that disrupts an interaction between said heterologous bait polypeptide and said prey polypeptide". As with claim 1 above, the examiner is unable to determine whether the prior art disclosure of the receptor taught by Eyckerman possesses the characteristic of being activated by addition of a compound that disrupts an interaction between the heterologous bait polypeptide and the prey polypeptide. With these conditions, where the product seems to be identical except that the prior art is silent to the characteristic or property claimed, then the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention.

Claim 11 is directed to a vector encoding the recombinant receptor of claim 1. Eyckerman teaches vectors encoding the receptors described above (pg 550, column 1). Therefore, claim 11 is also included in this rejection.

Claim 13 encompasses a eukaryotic cell comprising the receptor of claim 1. Eyckerman teaches rat PC12 cells transformed with the vectors described above (pg 550, column 1). Therefore, claim 13 is also included in this rejection.

Claim 16 is drawn to a "cloning vector encoding a recombinant receptor" that comprises "a nucleotide sequence encoding a cytoplasmic domain of a mammalian receptor" comprising "at least one restriction site configured to allow an in frame fusion of a nucleic acid sequence encoding a bait polypeptide, wherein insertion of the nucleic acid sequence encoding said bait polypeptide results in the vector of claim 11". The

vector sequence taught by Eyckerman already includes a 'bait polypeptide' (myc tag). However, the vector sequence inherently includes a restriction site near the C-terminus of the sequence encoding the leptin receptor, which if used to insert a sequence encoding another polypeptide (myc tag or other) would result in a vector that would still meet the limitations of claim 11. For example, the nucleic acid sequence encoding the murine leptin receptor includes the sequence 'CTCAAG' near the C-terminus of the receptor (see the record for GenBank Accession NM_14616, 6 pages, printed 1/16/08; cited previously), which is a recognition sequence for the restriction enzyme SmlI. Therefore, claim 16 is also included in this rejection.

Applicants' arguments (7/24/08; pg 5-7) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that the claims cannot be anticipated because Eyckerman does not teach every element of the claims; specifically, a bait polypeptide. Applicants argue that the myc-tag of the recombinant receptor taught by Eyckerman is not a heterologous bait polypeptide. Applicants argue that there is a "clear distinction" in the art "between a tag, such as a myc-tag, and a bait, the tag being a short peptide of only a few amino acids, intended as a marker, whereas a bait is a longer oligopeptide that forms a normal part of protein-protein interaction in a cellular system" (pg 8).

These arguments have been fully considered but are not found persuasive. The specification defines a ""heterologous bait polypeptide" as comprised in the receptor means that within the receptor, or fused to the receptor, but not in the ligand-binding domain of the receptor, there is a polypeptide that is not present in the non-recombinant receptor of which the cytoplasmic domain of the chimeric receptor is derived" and ""[b]ait" herein means that this polypeptide can interact with other polypeptides not belonging to the normal receptor complex" (¶ 64). Nothing in this definition excludes the heterologous myc-tag found in the receptor taught by Eyckerman. Furthermore, while Applicants argue that the skilled artisan would not consider a myc-tag to be a bait polypeptide, Applicants have not provided any evidence of such a distinction in the art.

As stated in MPEP 2145, "arguments of counsel cannot take the place of factually supported objective evidence".

Applicants further argue (pg 6) that the prey coupled to an inhibitor expressed in the claims is an essential element of the invention and Eyckerman does not disclose a prey polypeptide. Applicants argue that the skilled artisan "would have no knowledge (or motivation) that such a prey fusion construct could be used to inhibit the receptor" (pg 6). Applicants further argue that "even using the disclosure of the present application, it is unlikely that the Eyckerman receptor could be inhibited without burdensome experimentation in creating the anti-myc inhibitor fusion necessary" for such inhibition, and thus no reasonable expectation of success exists in modifying the teachings of Eyckerman to arrive at the present claims (pg 6).

Applicants' arguments have been fully considered but are not found persuasive. The instant claims do not require that the complete structure of the prey polypeptide of the inhibitory fusion protein is known prior to constructing a receptor that can be inhibited by said fusion protein. The instant specification discloses prior art methods for identifying bait-prey interactions (¶ 4-7 of the published application). Furthermore, Example 2 of the instant application references European patent application 00201771.3, which describes methods of screening libraries for prey molecules that interact with specific bait polypeptides. Thus, to meet the functional limitation of the claims, the recombinant receptor taught by Eyckerman only needs to be functionally capable of activation when contacted by any prey molecule that could be identified by the disclosed methods of screening with the bait polypeptide. Eyckerman itself does not teach whether or not the recombinant receptor taught therein would be inhibited by a fusion polypeptide comprising a prey molecule and at least one of an inhibitor of the activation selected from the group consisting of a member of the SOCS family, JAK-phosphatase and STAT-phosphatase. To meet this functional limitation, the recombinant receptor taught by Eyckerman only needs to be functionally capable of being inhibited when contacted by a fusion protein as recited in the claims. As far as the Examiner can determine, the specific mutant receptor described by Eyckerman would be inhibited if contacted with a fusion polypeptide such as those described in the instant

application (e.g., one comprising both a prey polypeptide that binds to myc and another one that comprises an inhibitor of activation). With these conditions, where the product seems to be identical except that the prior art is silent to the characteristic or property claimed, then the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Note the case law of *In re Best* 195 USPQ 430, 433 (CCPA 1977). Applicants have not provided any evidence that the recombinant receptor taught by Eyckerman would not be inhibited if used with a fusion polypeptide as recited in the instant claims. As stated in MPEP 2145, "arguments of counsel cannot take the place of factually supported objective evidence".

As set forth in the rejection, the rejected claims are directed to a genus of recombinant receptors, wherein the scope of the genus is partly defined by a functional interaction with a genus of fusion proteins comprising prey polypeptides and inhibitors of activation. The rejected claims are not directed to a fusion protein comprising a prey polypeptide *per se*, either alone or in combination with receptor. As such, the rejection of the claims under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Eyckerman et al, 1999 does not require that Eyckerman actually teach a fusion protein capable of inhibiting the receptor. If the receptor described by Eyckerman is inherently capable of being inhibited when contacted with a prey polypeptide recited in the claims, then it meets the recited functional limitations.

Applicants further argue that "[t]he myc-tag is a short peptide of 10 amino acids that can be bound by an antibody, but is generally incapable of binding to a normal protein by the classical protein-protein interaction normally associated with cellular function: although the tag is extensively used in the art, there are no protein-protein interactions described with the myc-tag other than myc-binding antibodies. Thus, inhibition of the myc-tagged protein of Eyckerman would only work through the cytoplasmic expression of a functional myc-binding antibody, fused to an inhibitor. It would have been clear to one of ordinary skill in the art that this would not work with classical heavy/light chain antibody complexes, as these are not found in the cytoplasm. If one of skill in the art attempted to develop a single chain antibody fused to an activation [sic, assumed "inhibitor"] domain, such development would not yield

predictable results, as the exact folding and requisite S-S bridge formation would be unpredictable for such a molecule without extensive experimentation. Moreover, even if one could obtain such a construct, it is unsure whether the activation domain, fused to such a single chain antibody, could inhibit the recombinant receptor in coordination while the anti-myc portion is bound to the myc-tag. Compared with the bait/prey interactions, the anti-myc antibody interaction would be a bulky complex where steric hindrance would be expected to prevent inhibition of the receptor. Thus, applicants respectfully submit that the receptors of Eyckerman cannot be inherently capable of being inhibited when contacted with an anti-myc/inhibitor fusion as the requisite anti-myc polypeptides have not been developed for intracellular use and there is no reasonable expectation of the successful function even if developed" (pg 6-7).

Applicants' arguments have been fully considered but are not found persuasive. Applicants provide no evidence supporting the assertion that the myc tag cannot be bound by any prey polypeptide other than an anti-myc antibody. As stated in MPEP 2145, "arguments of counsel cannot take the place of factually supported objective evidence". The Examiner does not dispute that it might be difficult to construct an antibody, even a single-chain antibody fusion, which functions as a prey molecule in the claims of the instant invention. However, the rejection of claim 1 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Eyckerman et al, 1999 does not require that the skilled artisan use an anti-myc antibody as part of the prey molecule. As noted above, the instant specification discloses prior art methods for identifying bait-prey interactions (¶ 4-7 of the published application). Furthermore, Example 2 of the instant application references European patent application 00201771.3, which describes methods of screening libraries for prey molecules that interact with specific bait polypeptides. Thus, there is no need to use an anti-myc antibody in the prey molecule. If the recombinant receptor taught by Eyckerman can be functionally activated by any single prey molecule (such as that identified from a library of prey molecules), then it meets the functional limitation of the claims. Eyckerman is silent as to whether the receptor has this functionality, thus the

burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention.

New rejections necessitated by Applicants' amendment

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter.

New claim 27 is directed to a "recombinant receptor complex" comprising a "recombinant receptor" and a "fusion protein" comprising a "prey polypeptide" and "an inhibitor of activation". The specification describes a recombinant receptor complex comprising a recombinant receptor and a fusion protein (as shown in Figure 1). The specification defines a prey polypeptide as "a fusion protein comprising one polypeptide that may bind with the heterologous bait polypeptide and another polypeptide that comprises an inhibitor of the receptor and/or a recruitment site for an inhibitor of the receptor" (¶ 65). Thus, the specification defines a prey polypeptide as the entire fusion protein in Figure 1, not just the portion that binds to the bait polypeptide. Thus, while the specification provides support for a complex comprising a fusion protein that is a prey molecule comprising a polypeptide that binds to the heterologous bait polypeptide and at least one of an inhibitor that is a member of the SOCS family, a JAK-phosphatase, and a STAT-phosphatase, the specification does not provide support for a complex comprising a fusion protein comprising a prey polypeptide and at least one of an inhibitor that is a member of the SOCS family, a JAK-phosphatase, and a STAT-phosphatase.

Claims 28-30 are included this rejection because they depend from claim 27 and encompass the same new matter.

Conclusion

No claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646